

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

Claim 1 (Currently Amended): ~~[[A]]~~ An isolated blood coagulation factor IX-activating protein derived from a mammal, which has an amino acid sequence of ~~SEQ ID NO: 4~~ SEQ ID NO: 4 and has the following properties:

- (1) the protein acts on blood coagulation factor IX to activate said factor;
- (2) the activity of the protein is inhibited in the presence of an α 1-protease inhibitor or soybean trypsin inhibitor;
- (3) the protein is present in erythrocyte membrane; and
- (4) the protein has a molecular weight of approximately 29 25.7 kDa as measured by SDS-PAGE.

Claim 2 (Original): The blood coagulation factor IX-activating protein according to claim 1 which cuts the amino acid sequence of the blood coagulation factor IX between 140th threonine and 141th serine, between 181th valine and 182th valine, and between 182th valine and 183th glycine.

Claim 3 (Original): The blood coagulation factor IX-activating protein according to claim 1 which is derived from human.

Claim 4 (Previously Presented): The blood coagulation factor IX-activating protein according to claim 1 which is purified by disrupting erythrocytes, extracting with a surfactant, and subjecting the extract to anion exchange chromatography and heparin affinity chromatography.

Claim 5 (Currently Amended): A pharmaceutical composition ~~medicine~~ which comprises a blood coagulation factor IX-activating protein according to claim 1.

Claim 6 (Currently Amended): The pharmaceutical composition ~~medicine~~ according to claim 5 ~~which is used~~ for treatment and/or prevention of diseases associated with abnormal blood coagulation.

Claim 7 (Canceled)

Claim 8 (Withdrawn): An antibody or fragment thereof which recognizes a blood coagulation factor IX-activating protein of claim 1.

Claim 9 (Withdrawn): The antibody or fragment thereof according to claim 8 wherein the antibody is a monoclonal antibody.

Claim 10 (Withdrawn – Currently Amended): A pharmaceutical composition ~~medicine~~ which comprises an antibody or fragment thereof of claim 8.

Claim 11 (Withdrawn – Currently Amended): The pharmaceutical composition ~~medicine~~ according to claim 10 ~~which is used~~ for treatment and/or prevention of diseases associated with abnormal blood coagulation.

Claim 12 (Withdrawn): A labeled antibody or fragment thereof which recognizes a blood coagulation factor IX-activating protein of claim 1.

Claim 13 (Withdrawn – Currently Amended): A pharmaceutical composition ~~medicine~~ which comprises a labeled antibody or fragment thereof of claim 12.

Claim 14 (Withdrawn – Currently Amended): The pharmaceutical composition ~~medicine~~ according to claim 13 which is a diagnostic drug for diseases associated with blood coagulation.

Claim 15 (Withdrawn): A method for detecting a blood coagulation factor IX-activating ability which comprises detecting or measuring a blood coagulation factor IX-activating protein of claim 1 in a biological sample.

Claim 16 (Withdrawn – Currently Amended): A method for evaluating a risk of blood coagulation in a subject with diabetes, pregnancy or aging, which comprises ~~a step~~ of determining the degree of activation of a blood coagulation factor IX by the blood coagulation factor IX-activating protein of claim 1 in erythrocytes in a subject.

Claim 17 (Withdrawn – Currently Amended): The method according to claim 16 wherein the degree of activation of a blood coagulation factor IX is determined by determining the time of onset of coagulation of a mixture of erythrocytes (RBCs) and platelet free plasma (PFP) which was prepared from a blood of a subject.

Claim 18 (Withdrawn): A peptide consisting of an amino acid sequence from 141th serine to 181th valine of a blood coagulation factor IX.

Claim 19 (Withdrawn): The peptide consisting of an amino acid sequence from 141th serine to 181th valine of a blood coagulation factor IX which is obtained by treating a blood coagulation factor IX with the blood coagulation factor IX-activating protein according to claim 1.

Claim 20 (Withdrawn – Currently Amended): A method for screening an inhibitor for the blood coagulation factor IX-activating protein according to claim 1, wherein ~~said~~ the blood coagulation factor IX-activating protein is ~~used~~ combined with a candidate inhibitor.

Claim 21 (Withdrawn – Currently Amended): A method for screening an inhibitor for the blood coagulation factor IX-activating protein according to claim 1 ~~wherein said blood coagulation factor IX-activating protein is used,~~ and wherein a fluorogenic synthetic substrate, the blood coagulation factor IX-activating protein according to claim 1 and a candidate inhibitor are mixed and incubated, and then the fluorescence intensity is measured.

Claim 22 (Withdrawn – Currently Amended): The method according to claim 21, wherein the fluorogenic synthetic substrate is Suc(OMe)-Ala-Ala-Pro-Val-MCA (SEQ ID NO: 7).

Claim 23 (Withdrawn – Currently Amended): A method for inhibiting the activation of a blood coagulation factor IX by the blood coagulation factor IX-activating protein comprising administering an inhibitor which is obtained by the method according to claim 20, the blood coagulation factor IX-activating protein being derived from a mammal, which has an amino acid sequence of ~~SEQ ID NO: 4~~ SEQ ID NO: 4 and having the following properties:

- (1) the protein acts on blood coagulation factor IX to activate said factor;
- (2) the activity of the protein is inhibited in the presence of an α 1-protease inhibitor or soybean trypsin inhibitor;
- (3) the protein is present in erythrocyte membrane; and

(4) the protein has a molecular weight of approximately 29 25.7 kDa as measured by SDS-PAGE; and

~~wherein the inhibitor which is obtained by the method of according to claim 20 is used.~~

Claim 24 (Withdrawn – Currently Amended): A method for analyzing the activity of the blood coagulation factor IX-activating protein of claim 1 which comprises ~~steps of~~ (a) providing a substrate which can not be cleaved with esterase but can be cleaved with the blood coagulation factor IX-activating protein of claim 1, and which is obtained by substituting the amino acid(s) of the cleavage site of a blood coagulation factor IX which is cleaved by esterase only, with another amino acid(s); (b) reacting the substrate with the blood coagulation factor IX-activating protein of claim 1; and (c) detecting the substrate which was cleaved with the blood coagulation factor IX-activating protein of claim 1.

Claim 25 (New): A method for activating blood coagulation factor IX in a mammal which comprises administering an activating effective amount of an isolated blood coagulation factor IX-activating protein derived from a mammal, which has an amino acid sequence of SEQ ID NO: 4 and has the following properties:

- (1) the protein acts on blood coagulation factor IX to activate said factor;
- (2) the activity of the protein is inhibited in the presence of an α 1-protease inhibitor or soybean trypsin inhibitor ;
- (3) the protein is present in erythrocyte membrane ;
- (4) the protein has a molecular weight of approximately 25.7 kDa as measured by SDS-PAGE .

Claim 26 (New): The method for activating blood coagulation factor IX in a mammal according to claim 25 in which the blood coagulation factor IX-activating protein cuts the amino acid sequence of the blood coagulation factor IX between 140th threonine and 141th serine, between 181th valine and 182th valine, and between 182th valine and 183th glycine.

Claim 27 (New): The method for activating blood coagulation factor IX in a mammal according to claim 26 in which the blood coagulation factor IX-activating protein is derived from a human.

Claim 28 (New): The method for activating blood coagulation factor IX in a mammal according to claim 26 in which the blood coagulation factor IX-activating protein is included in a pharmaceutical composition.

Claim 29 (New): The method for activating blood coagulation factor IX in a mammal according to claim 28 comprising at least one of treatment or prevention of a disease associated with abnormal blood coagulation.